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A short synthesis of the anti-leukemic sesquiterpene (+)-caparratriene employing aqueous Wittig chemistry

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ABSTRACT

An efficient, stereoselective method for the synthesis of (+)-caparratriene based on an aqueous Wittig reaction has been developed. A functionalized triethylallyl ylide reacted under various conditions with (+)-citronellal to deliver (+)-caparratriene in only three steps with excellent overall yield. The Wittig reaction proceeded with exclusive (4*E*)-selectivity and an interesting cationic effect was uncovered with good stereoselectivity at the isomerizable allylic position being observed in the presence of lithium salts.

1. Introduction

Conjugated 1,3-diene and 1,3,5-triene functional groups are common sub-units found in a wide range of natural products usually of fatty acid or isoprenoid origin.[1] These compounds are endowed with a wide range of biological activities including antimicrobial, anticancer as well as hormonal and pheromonal activity to name a few. A selection of examples is collected in Figure 1.

We were attracted to the naturally occurring sesquiterpene (+)-caparratriene **6**[2] as a synthetic target based upon its reported anticancer activity. (+)-Caparratriene was isolated in 1996 from the resin of the Colombian tree *Ocotea caparrapi* (Lauraceae), based on ethnopharmacological usage of the resin in the treatment of a range of ailments including tumors. The active principle was identified as (+)-caparratriene **6** by Palomino et al. who documented its anti-cancer activity ($IC_{50} = 3.0 \pm 0.5 \times 10^{-6}$ M) against human leukemic cell lines (CEM).[2]

We recently reported the stereoselective synthesis of a range of conjugated 1,3-dienes and 1,3,5-trienes[3a] employing the aqueous Wittig reaction of semi-stabilized ylides.[3] In this work, we showed that the use of *triethyl*-substituted semi-stabilized ylides leads to higher ratios of (*E*)-olefins upon reaction with a range of aldehydes.[4] The triethylphosphine oxide side-product is also readily removed form this process due to its high water solubility. Natural (+)-caparratriene has been synthesized only once before, employing a low yielding cross-McMurry olefination reaction of two aldehydes to construct the *trans*-C4 to C5 double bond.[5a] A racemic synthesis has also been reported that utilized a Suzuki cross-coupling to construct the C3 to C4 sp^2–sp^2 bond.[5b] In our analysis (Fig. 2), (+)-caparratriene should be available directly from commercially available (+)-citronellal employing an aqueous Wittig olefination with the semi-stabilized ylide shown. The precursor phosphonium salt should be available from the allylic alcohol **8**, leading back to readily available (*E*)-aldehyde **7**. In this Letter we report a direct three-step synthesis of (+)-caparratriene following this approach.

2. Results and discussion

Commercially available aldehyde **7** was reduced without event to the allylic alcohol **8**, Scheme 1. The synthesis of allylic triphenylphosphonium salts from allylic alcohols and acidic Ph_3P–HBr was reported by chemists at BASF in the late 1950's in the synthesis vitamin A and analogues.[6] It is not obvious that triethylphosphine hydrobromide ($pK_a = 8.69$)[6d] would be acidic enough to allow the conversion of allylic alcohols to their corresponding phosphonium salt. Triethylphosphine hydrobromide was prepared directly from the reaction of triethylphosphine with 47% HBr. The salt is a hygroscopic, colorless crystalline solid, stable to aerial oxidation upon direct exposure to open laboratory conditions over several weeks. In addition, the salt is almost odorless and proved easy to handle.

To our delight, we found that the allylic alcohol **8** could be directly converted to the triethylphosphonium salt **9** in the presence of Et_3P–HBr via conventional thermal heating (100 °C, 8 h), or more conveniently through microwave irradiation. Under microwave irradiation, the reaction was completed in 10 min (100 °C, sealed tube).[7] This method circumvents the need to work directly with triethylphosphine and reactive, hazardous allylic alkylating agents in the synthesis of phosphonium salts of type **9**.

The Wittig reaction of semi-stabilized ylides with aliphatic aldehydes generally results in poor configurational selectivity.[8] In our recent Letter, we showed that the use of triethylallylphosphoranes can result in significantly higher levels of (*E*)-stereoselectivity.[3a,4] We thus expected to obtain olefins in the present case with high (4*E*)-stereocontrol. In terms of the required 2*E*/2*Z* stereocontrol,

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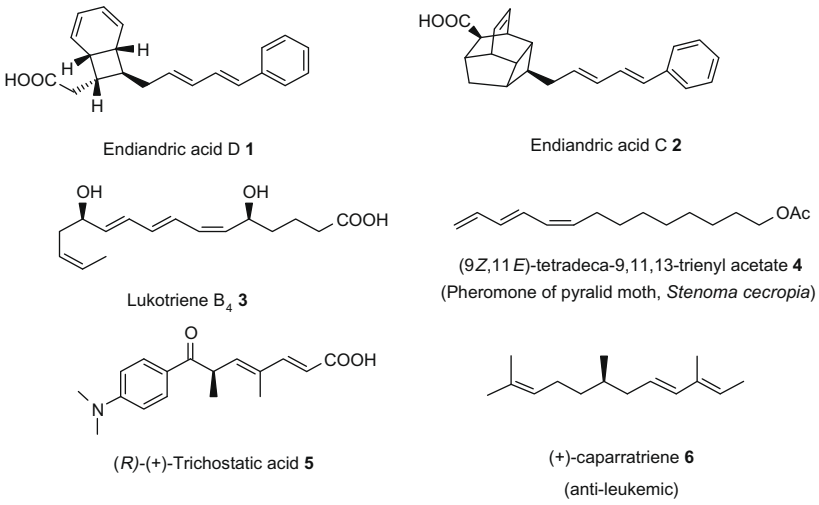


Figure 1. Selected naturally occurring bioactive 1,3-dienes and 1,3,5-trienes.

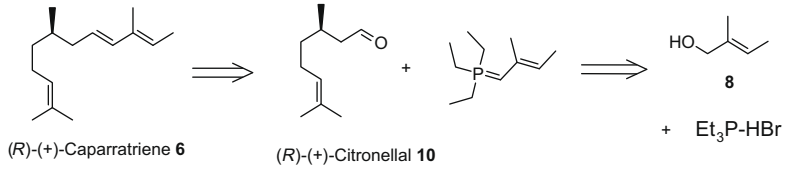
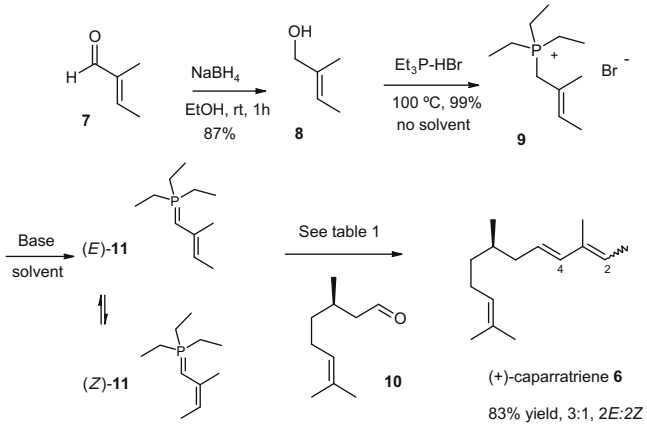


Figure 2. (+)-Caparratriene retrosynthetic analysis.



Scheme 1. Synthesis of (+)-caparratriene **6**.

the reaction of (*E*)-β,γ-unsaturated ylides is known to provide 1,3-dienes with retention of stereochemistry at the allylic double bond.[9] However, the reaction of (*Z*)-β,γ-unsaturated ylides can lead to isomerization around the allylic double bond. This factor complicates the reaction of ylide (*E*)-**11** since relief of torsional and non-bonding interactions between the two methyl groups could promote isomerization to (*Z*)-**11** (Scheme 1). In the reaction with citronellal, this isomerization would result in loss of stereocontrol and the formation of 2*E* and 2*Z*-steroisomers of **6**. A challenge in the present case was recognized as prevention of this allylic isomerization on the ylide **11**.

In our initial Wittig attempt, the ylide generated from **9** in dry THF using potassium hexamethyldisilazide (KHMDS) as a base, reacted with citronellal **10** to give a 50:50 mixture of both 2*E* and 2*Z* isomers (Table 1, entry 1). Importantly, however, was the exclusive

Table 1
Reaction of the ylide derived from **9** with (+)-citronellal under various conditions

Entry	Base	Solvent	Temp (°C)	Time (h)	**6** Yield (%)	2*E*:2*Z*
1	KHMDS	THF	0	3	74	1:1
2	NaHMDS	THF	0	3	76	2:1
3	LiHMDS	THF	0	3	77	2.5:1
4	NaOH	H_2O	rt	13	80	1.5:1
5	NaOH	H_2O	70	3	79	1.5:1
6	NaOH, LiCl	H_2O	rt	13	78	2:1
7	NaOH, LiCl	H_2O	70	3	77	2:1
8	LiOH	H_2O	rt	13	83	2:1
9	LiOH	H_2O	70	3	80	2:1
10	LiOH, LiCl	H_2O	rt	13	78	3:1
11	LiOH, LiCl	H_2O	70	3	77	3:1

formation of only the 4*E*-stereoisomers observed on the Wittig reaction itself, as evidenced by the downfield chemical shift and coupling constant (15.6 Hz) for H4 in both isomers.[7] In view of the low 2*E*:2*Z* stereocontrol, the reaction of ylide **11** derived from **9** with (+)-citronellal **10** was investigated under a range of aqueous and non-aqueous conditions with a variety of different bases and in the presence of various alkali metal salts. The results on the stereoselectivity of this olefination are summarized in Table 1. With THF as a solvent, more of the desired 2*E* isomer was produced in the presence of sodium and furthermore proceeding to lithium salts (entries 2 and 3), indicating some form of chelation effect. Moving to the aqueous Wittig reaction, the reaction again proceeded with exclusive 4*E*-stereocontrol and with moderate 2*E*-stereocontrol (entries 4–9). Overall, a significant cationic effect was observed, with higher levels of (*E*)-olefin selectivity seen in the presence of lithium ions. Finally, the use of a combination of lithium hydroxide as a base in water in conjunction with added lithium chloride at room temperature (13 h) proved to give the optimal yield and level of highest level of 2*E*-stereocontrol (entries

10 and 11), again with exclusive 4*E*-stereocontrol. These conditions were superior to the best non-aqueous result (entry 3). We speculate that the present cationic effect may be attributed to coordination of this electron rich allylic phosphorane to the cation ($Li^+ > Na^+ > K^+$), hindering the (*E*)-**11** to (*Z*)-**11** isomerization.[10]

Lastly, the entire process from the allylic alcohol **8** could be conducted in a single two-stage operation involving first microwave irradiation with Et_3P–HBr to give **9**, followed by the addition of aqueous LiOH/LiCl and (+)-citronellal giving (+)-caparratriene **6** in about 70% overall isolated yield with exclusive 4*E*-stereocontrol as a 3:1 mixture of the 2*E*:2*Z* isomers.

3. Conclusion

In conclusion, we report a direct synthesis of a functionalized triethylallylic phosphonium salt directly from the reaction of a functionalized allylic alcohol and triethylphosphine hydrobromide. The ylide derived from this salt reacts with (+)-citronellal in aqueous media to give the natural 1,3-diene (+)-caparratriene. The Wittig reaction proceeds with exclusive (4*E*)-olefin configurational selectivity. The level of allylic (2*E*)-olefin stereoselectivity was subject to a cationic effect with higher levels of the 2*E*-olefin being observed in the presence of lithium salts. Further applications of this aqueous Wittig protocol toward the synthesis of a range of (+)-caparratriene analogues and an investigation of their anticancer activity are under investigation.

Acknowledgments

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7. *Representative procedures*: (a) *Synthesis of 1-(2E,2-methylbutenyl)triethylphosphonium bromide* **9**: Into a flame-dried microwave vial, containing a magnetic stirring bar, was weighed the allylic alcohol **8** (172.3 mg, 2 mmol, 1 equiv) under Ar. Triethylphosphine hydrobromide (396.1 mg, 2 mmol, 1 equiv) was added to the vial. The vial was septa-sealed and heated in the microwave for 10 min at 100 °C. The septa was removed and kept under high vacuum for 1 h to give the title compound **9**, 526.9 mg, (99%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (m, 9H), 1.55 (s, 3H), 1.75 (s, 3H), 2.45 (m, 6H), 3.34 (d, J_{PC} = 15.2 Hz, 2H), 5.65 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 5.8 (d, J_{PC} = 5 Hz), 12.2 (d, J_{PC} = 48.0 Hz), 12.3, 13.3, 28.7 (d, J_{PC} = 44.5 Hz), 122.7 (d, J_{PC} = 10.5 Hz), 128.7 (d, J_{PC} = 10.9 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): 35.4; HRES MS $(M)^+$ calcd for $C_{11}H_{24}P$: 187.1616, found 187.1597.
(b) *Synthesis of (R)-(+)-caparratriene* **6**: Into a flame-dried flask, containing a magnetic stirring bar, was weighed 1-(2*E*,2-methylbutenyl)triethylphosphonium bromide **9** (266 mg, 1 mmol, 1 equiv) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon LiOH (24 mg, 1 mmol, 1 equiv) and LiCl (42 mg, 1 mmol, 1 equiv) were added sequentially. After 2 min (*R*)-(+)-citronellal (181.3 μL, 1 mmol, 1 equiv) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. Five milliliters of water were added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (hexane) to yield the title compound **6**, 158.8 mg, (77%) as a colorless oil. Data for the (2*E*,4*E*) isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (d, *J* = 7.0 Hz, 3H), 1.15 (m, 1H), 1.36 (m, 1H), 1.51 (m, 1H), 1.60 (s, 3H), 1.69 (s, 3H), 1.71 (d, *J* = 7.0 Hz, 3H), 1.73 (s, 3H), 1.97 (m, 3H), 2.10 (m, 1H), 5.10 (m, 1H), 5.43 (q, *J* = 7.0 Hz, 1H), 5.52 (dt, *J* = 7.7 Hz, 15.6 Hz, 1H), 6.04 (d, *J* = 15.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.1, 13.8, 17.8, 19.6, 25.8, 25.9, 33.2, 36.9, 40.4, 124.5, 125.0, 125.9, 131.2, 134.9, 135.9; HRCI MS $(M)^+$ calcd for $C_{15}H_{26}$: 206.2035, found 206.2035. Data for the (2*Z*,4*E*) isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.89 (d, *J* = 7.0 Hz, 3H), 1.15 (m, 1H), 1.36 (m, 1H), 1.51 (m, 1H), 1.52 (s, 3H), 1.72 (d, *J* = 7.0 Hz, 3H), 1.76 (s, 3H), 1.80 (s, 3H), 1.97 (m, 3H), 2.14 (m, 1H), 5.10 (m, 1H), 5.65 (q, *J* = 7.0 Hz, 1H), 5.86 (dt, *J* = 7.7 Hz, 15.6 Hz, 1H), 6.43 (d, *J* = 15.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.2, 13.0, 17.6, 20.8, 25.8, 25.9, 33.3, 36.7, 40.9, 122.6, 125.0, 128.1, 129.2, 133.0, 133.8; HRCI MS $(M)^+$ calcd for $C_{15}H_{26}$: 206.2035, found 206.2035.
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